

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 11 July 2001 (11.07.01)	
International application No. PCT/US00/27443	Applicant's or agent's file reference DC-0141
International filing date (day/month/year) 04 October 2000 (04.10.00)	Priority date (day/month/year) 06 October 1999 (06.10.99)
Applicant HAMILTON, Joshua, W. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 01 May 2001 (01.05.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25400 A2

- (51) International Patent Classification⁷: C12N
- (21) International Application Number: PCT/US00/27443
- (22) International Filing Date: 4 October 2000 (04.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/158,000 6 October 1999 (06.10.1999) US
60/194,274 3 April 2000 (03.04.2000) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:
US 60/158,000 (CIP)
Filed on 6 October 1999 (06.10.1999)
US 60/194,274 (CIP)
Filed on 3 April 2000 (03.04.2000)
- (71) Applicant (for all designated States except US):
TRUSTEES OF DARTMOUTH COLLEGE [US/US];
Technology Transfer Office, 11 Rope Ferry Road, Hanover,
NH 03755-1404 (US).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): **HAMILTON, Joshua, W.** [US/US]; 38 Laramie Road, Etna, NH 03750 (US). **STANTON, Bruce, A.** [US/US]; 26 Low Road, Hanover, NH 03755 (US).
- (74) Agents: **LICATA, Jane, Massey et al.**; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).
- (81) Designated States (national): CA, JP, US.
- (84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR MODULATING ATP-BINDING CASSETTE TRANSMEMBRANE REPORTER PROTEIN EXPRESSION

(57) Abstract: Methods and compositions for modulating cell surface protein expression are provided. The compositions of the present invention are gene constructs comprising ATP-binding cassette transmembrane reporter proteins.

WO 01/25400 A2

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25400 A3

- (51) International Patent Classification⁷: C12Q 1/68, A61K 48/00, 49/00, C12P 21/06, C12N 5/00, 15/00
- (72) Inventors; and
(75) Inventors/Applicants (for US only): HAMILTON, Joshua, W. [US/US]; 38 Laramie Road, Etna, NH 03750 (US). STANTON, Bruce, A. [US/US]; 26 Low Road, Hanover, NH 03755 (US).
- (21) International Application Number: PCT/US00/27443
- (22) International Filing Date: 4 October 2000 (04.10.2000)
- (74) Agents: LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).
- (25) Filing Language: English
- (26) Publication Language: English
- (81) Designated States (national): CA, JP, US.
- (30) Priority Data:
60/158,000 6 October 1999 (06.10.1999) US
60/194,274 3 April 2000 (03.04.2000) US
- (84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:
US 60/158,000 (CIP)
Filed on 6 October 1999 (06.10.1999)
US 60/194,274 (CIP)
Filed on 3 April 2000 (03.04.2000)
- Published:
— with international search report
- (88) Date of publication of the international search report:
30 August 2001
- (71) Applicant (for all designated States except US):
TRUSTEES OF DARTMOUTH COLLEGE [US/US];
Technology Transfer Office, 11 Rope Ferry Road, Hanover,
NH 03755-1404 (US).
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(57) Abstract: Methods and compositions for modulating cell surface protein expression are provided. The compositions of the present invention are gene constructs comprising ATP-binding cassette transmembrane reporter proteins.

WO 01/25400 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27443

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A61K 48/00, 49/00; C12P 21/06; C12N 5/00, 15/00

US CL : 435/6, 172.1, 320.1; 535/23.7, 16.8; 424/93.2; 514/283

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 172.1, 320.1; 535/23.7, 16.8; 424/93.2; 514/283

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG, C. et al. Expression and purification of the first nucleotide-binding domain and linker region of human multidrug resistance gene product: comparison of fusions to glutathione S-transferase, thioredoxin and maltose-binding protein. Biochem. J. 1999, Vol. 338, pages 77-81, whole document.	1-11
X,P	CHEN, Y. et al. In situ biochemical demonstration that P-Glycoprotein is a drug efflux pump with broad specificity. The J. of Cell Biol. 06 March 2000, Vol., 148, No. 5, pages 863-70, whole document.	1-11
X	KOLLEN, W. et al. High-efficiency transfer of cystic fibrosis transmembrane conductance regulator cDNA into cystic fibrosis airway cells in culture using lactosylated polylysine as a vector. Human Gene Therapy. 01 March 1999, Vol. 10, pages 615-22, abstract.	1-2 -----
Y	US 5,972,598 A (CHAUDHARY) 26 October 1999, abstract.	3-11
Y	US 6,093,567 A (GREGORY) 25 July 2000, whole document.	3, 6-11
Y,P	AKABAS, M. Channel-linking residues in the M3 membrane-spanning segment of the cystic fibrosis transmembrane conductance regulator. Biochemistry. 1998, Vol. 37, No. 35, whole document.	4, 5

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

19 January 2001 (19.01.2001)

Date of mailing of the international search report

04 APR 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

GEETHA BANSAL

Telephone No. 703-308-1234

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27443

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☒

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27443

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I claim(s) 1-2, drawn to a DNA construct comprising CFTR-EGFP.

Group II, claim(s) 3, drawn to a DNA construct comprising MDRI-Pgp-EGFP.

Group III, claim(s) 4-5, drawn to a DNA construct comprising a mutant CFTR-EGFP.

Group IV, claim(s) 6, drawn to a cell line.

Group V, claim(s) 7, drawn to a method of using MDRI-Pgp-EGFP construct to screen agents.

Group VI, claim(s) 8, drawn to a method of using MDRI-Pgp-EGFP construct to identify agents that alter the MDRI phenotype.

Group VII, claim(s) 9, drawn to a method of using MDRI-Pgp-EGFP construct to screen agents for the treatment of cystic fibrosis.

Group VIII, claim(s) 10-11, drawn to a method of treating cystic fibrosis.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of the invention surrounds a DNA construct comprising a CFTR-EGFP. It was found by the examiner that the claimed construct does not have significant contribution over the prior art. The claimed construct has previously been disclosed by Kollen et al (see abstract).

Continuation of B. FIELDS SEARCHED Item 3: MEDLINE

keywords: cystic fibrosis and multi-drug resistance gene and cancer OR CFTR and MDRI and GFP construct

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

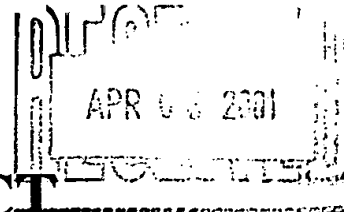
If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY



From the INTERNATIONAL SEARCHING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

Docket System ☒
Status Report ☒
Docket Book ☒

6/4/01 MJS

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

04 APR 2001

Applicant's or agent's file reference
DC-0141

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US00/27443

International filing date
(day/month/year)

04 October 2000 (04.10.2000)

Applicant
TRUSTEES OF DARTMOUTH COLLEGE

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompany sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer

Geetha Bansal
GEETHA BANSAL

Telephone No. 703-308-1234

PATENT COOPERATION TREATY

M

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

04 APR 2001

Applicant's or agent's file reference
DC-0141

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US00/27443

International filing date
(day/month/year)

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Name and mailing address of the ISA/US
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Facsimile No. (703)305-3230

Authorized officer

Geetha Bansal
GEETHA BANSAL

Telephone No. 703-308-1234

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DC-0141	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/27443	International filing date (<i>day/month/year</i>) 04 October 2000 (04.10.2000)	(Earliest) Priority Date (<i>day/month/year</i>) 06 October 1999 (06.10.1999)
Applicant TRUSTEES OF DARTMOUTH COLLEGE		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27443

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☒

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27443

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A61K 48/00, 49/00; C12P 21/06; C12N 5/00, 15/00

US CL : 435/6, 172.1, 320.1; 535/23.7, 16.8; 424/93.2; 514/283

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 172.1, 320.1; 535/23.7, 16.8; 424/93.2; 514/283

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG, C. et al. Expression and purification of the first nucleotide-binding domain and linker region of human multidrug resistance gene product: comparison of fusions to glutathione S-transferase, thioredoxin and maltose-binding protein. Biochem. J. 1999, Vol. 338, pages 77-81, whole document.	1-11
X,P	CHEN, Y. et al. In situ biochemical demonstration that P-Glycoprotein is a drug efflux pump with broad specificity. The J. of Cell Biol. 06 March 2000, Vol., 148, No. 5, pages 863-70, whole document.	1-11
X	KOLLEN, W. et al. High-efficiency transfer of cystic fibrosis transmembrane conductance regulator cDNA into cystic fibrosis airway cells in culture using lactosylated polylysine as a vector. Human Gene Therapy. 01 March 1999, Vol. 10, pages 615-22, abstract.	1-2 -----
Y	US 5,972,598 A (CHAUDHARY) 26 October 1999, abstract.	3-11
Y	US 6,093,567 A (GREGORY) 25 July 2000, whole document.	3, 6-11
Y,P	AKABAS, M. Channel-linking residues in the M3 membrane-spanning segment of the cystic fibrosis transmembrane conductance regulator. Biochemistry. 1998, Vol. 37, No. 35, whole document.	4, 5

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 January 2001 (19.01.2001)

Date of mailing of the international search report

04 APR 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Geetha Bansal

Telephone No. 703-308-1234

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I claim(s) 1-2, drawn to a DNA construct comprising CFTR-EGFP.

Group II, claim(s) 3, drawn to a DNA construct comprising MDRI-Pgp-EGFP.

Group III, claim(s) 4-5, drawn to a DNA construct comprising a mutant CFTR-EGFP.

Group IV, claim(s) 6, drawn to a cell line.

Group V, claim(s) 7, drawn to a method of using MDRI-Pgp-EGFP construct to screen agents.

Group VI, claim(s) 8, drawn to a method of using MDRI-Pgp-EGFP construct to identify agents that alter the MDRI phenotype.

Group VII, claim(s) 9, drawn to a method of using MDRI-Pgp-EGFP construct to screen agents for the treatment of cystic fibrosis.

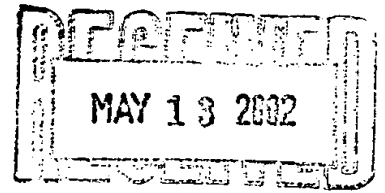
Group VIII, claim(s) 10-11, drawn to a method of treating cystic fibrosis.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of the invention surrounds a DNA construct comprising a CFTR-EGFP. It was found by the examiner that the claimed construct does not have significant contribution over the prior art. The claimed construct has previously been disclosed by Kollen et al (see abstract).

Continuation of B. FIELDS SEARCHED Item 3: MEDLINE

Keywords: cystic fibrosis and multi-drug resistance gene and cancer OR CFTR and MDRI and GFP construct

PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

~~Docket System~~
~~Status Report~~
~~Docket Book~~

NP = 4-6-02

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year) **09 MAY 2002**

Applicant's or agent's file reference

DC-0141

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US00/27443

04 October 2000 (04.10.2000)

06 October 1999 (06.10.1999)

Applicant

TRUSTEES OF DARTMOUTH COLLEGE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Stephen L. Rawlings, Ph.D.

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DC-0141		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/27443	International filing date (day/month/year) 04 October 2000 (04.10.2000)	Priority date (day/month/year) 06 October 1999 (06.10.1999)	
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 48/00, 49/00; C12N 5/00, 15/00; C12P 21/06; C12Q 1/68 and US Cl.: 424/93.2; 435/6, 172.1, 320.1; 514/283; 535/23.7, 16.8			
Applicant TRUSTEES OF DARTMOUTH COLLEGE			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 04 May 2001 (01.05.2001)		Date of completion of this report 02 November 2001 (02.11.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer <i>Stephen L. Rawlings</i> For Stephen L. Rawlings, Ph.D. Telephone No. (703) 308-0196	

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/27443

I. Basis of the report**1. With regard to the elements of the international application:***

the international application as originally filed.



the description:

pages 1-23 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the claims:

pages 24-26 as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the drawings:

pages NONE as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____



the sequence listing part of the description:

pages NONE as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:



the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).



the language of publication of the international application (under Rule 48.3(b)).



the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

contained in the international application in printed form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

the description, pages NONE



the claims, Nos. NONE



the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/27443

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☒ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

Please See Continuation Sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-6

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/27443**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-6</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-6</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-6</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-6 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the claimed subject matter. Claims 1, 2, 4, and 5 are drawn to a genetic construct comprising a cDNA encoding an ABC gene linked at the 5' end to a cDNA encoding a reporter gene, wherein expression is regulated by proximal promoter region of the ABC gene (claim 1), wherein said ABC gene encodes a human CFTR and said reporter gene encodes EGFP (claim 2), wherein said CFTR is a mutant CFTR (claim 4), wherein said mutant CFTR is $\Delta F508$ (claim 5). Claim 3 is drawn to the genetic construct of claim 1 wherein the ABC gene encodes human Pgp. Claim 6 is drawn to a cell line transfected with the genetic construct of claim 1. The prior art cited in the International Search Report mailed on 04 April 2001 does not teach or fairly suggest all of the limitations of the claims. For that reason, the prior art does not teach or fairly suggest the subject matter of the claims. Furthermore claims 1-6 have industrial applicability. Therefore, claims 1-6 satisfy the criteria set out in PCT Article 33(2)-(4).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/27443

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

IV. 3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-6, drawn to a genetic construct comprising a cDNA for an ABC reporter gene linked to a cDNA for a reporter gene under regulation of a proximal promoter region of the reporter gene and a cell line transfected with said genetic construct.

Group II, claim(s) 7 and 8, drawn to a method for assessing the ability of antineoplastic agents to induce multi-drug resistance in tumor cells transfected with the genetic construct of claim 1.

Group III, claim(s) 9, drawn to a method for identifying agents for use in the treatment of cystic fibrosis.

Group IV, claim(s) 10 and 11, drawn to a method for treating patients diagnosed with cystic fibrosis.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature linking Groups I-IV appears to be a genetic construct according to claim 1. However, Kollen, et al (Human Gene Therapy 10: 615-622, 1999) teach the claimed genetic construct and therefore the technical feature linking the inventions in Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is a genetic construct.

The special technical feature of Group II is exposing cells transfected with a genetic construct according to claim 1 to an antineoplastic agent and monitoring transcription of the *MDRI* gene.

The special technical feature of Group III is exposing cells transfected with a genetic construct according to claim 1 to an agent suspected of being useful in treatment of cystic fibrosis and measuring CTFR expression levels or trafficking of CFTR to the cell membrane of the exposed cells.

The special technical feature of Group IV is administering an agent to a pateint with cystic fibrosis.

Accordingly, Groups I-IV are not so linked by the same or corresponding special technical feature as to form a single general inventive concept.

CHAPTER II
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION



PCT No.: PCT/US00/27443

Examiner: Stephen L. Rawlings, Ph.D.

Attorney spoken to: Jane Massey Licata

Date of call: 02 November 2001

- ☐ Amount of payment approved:
- ☐ Deposit account number to be charged:
- ☐ Attorney elected to pay for ALL additional inventions
- ☐ Attorney elected to pay only for the additional inventions covered by
- ☐ Group(s):
- encompassing --
- ☐ Claim(s):
- ☒ Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention Group I, covered by Claim(s) 1-6 has been examined.
- ☒ Attorney was orally advised that there is no right to protest for any group not paid for.
- ☒ Attorney was orally advised that any protest must be filed no later than 1 Month from the mailing of the Opinion (Form PCT/IPEA/408) or the Final Report (Form PCT/IPEA/409).

Time Limit For Filing A Protest

Applicant is hereby given 1 Month from the mailing date of this Opinion/Final Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 68.3, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Itemized Summary of Claim Groupings:

Please See Continuation Sheet

Detailed Reasons For Holding Lack of Unity of Invention:

Please See Continuation Sheet

Note: A copy of this form must be attached to the Opinion/Final Report.

ATTACHMENT TO CHAPTER II PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Itemized Summary of Claim Groupings:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-6, drawn to a genetic construct comprising a cDNA for an ABC reporter gene linked to a cDNA for a reporter gene under regulation of a proximal promoter region of the reporter gene and a cell line transfected with said genetic construct.

Group II, claim(s) 7 and 8, drawn to a method for assessing the ability of antineoplastic agents to induce multi-drug resistance in tumor cells transfected with the genetic construct of claim 1.

Group III, claim(s) 9, drawn to a method for identifying agents for use in the treatment of cystic fibrosis.

Group IV, claim(s) 10 and 11, drawn to a method for treating patients diagnosed with cystic fibrosis.

Detailed Reasons For Holding Lack of Unity of Invention:

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature linking Groups I-IV appears to be a genetic construct according to claim 1. However, Kollen, et al (Human Gene Therapy 10: 615-622, 1999) teach the claimed genetic construct and therefore the technical feature linking the inventions in Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is a genetic construct.

The special technical feature of Group II is exposing cells transfected with a genetic construct according to claim 1 to an antineoplastic agent and monitoring transcription of the *MDR1* gene.

The special technical feature of Group III is exposing cells transfected with a genetic construct according to claim 1 to an agent suspected of being useful in treatment of cystic fibrosis and measuring CFTR expression levels or trafficking of CFTR to the cell membrane of the exposed cells.

The special technical feature of Group IV is administering an agent to a patient with cystic fibrosis.

Accordingly, Groups I-IV are not so linked by the same or corresponding special technical feature as to form a single general inventive concept.

Note: A copy of this form must be attached to the Opinion/Final Report.